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In re Application of :

Dr. Sonja LIEB et al.

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SUBMISSION OF PRIORITY DOCUMENT(S)

Commissioner for Patents
P.O. Box 1450
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Sir:

Submitted herewith is a certified copy of each of the below-identified document(s), benefit of priority of each of which is claimed under 35 U.S.C. § 119:

COUNTRY	APPLICATION NO.	FILING DATE
EP	03028222.2	12/09/2003

Acknowledgment of the receipt of the above document(s) is requested.

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Respectfully submitted,

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Blvd. Suite 1400
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Anmelder/Applicant(s)/Demandeur(s):

Helm AG
Nordkanalstrasse 28
20097 Hamburg
ALLEMAGNE

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Pharmaceutical formulation of valaciclovir

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LEDERER & KELLER

Patentanwälte - European Patent Attorneys
European Trademark Attorneys

DR. A. VAN DER WERTH
(1934 - 1974)

DR. FRANZ LEDERER
Dipl.-Chem.

DR. GÜNTER KELLER
Dipl.-Biol.

DR. MICHAEL BEST
Dipl.-Chem.

DR. STEPHAN TEIPEL
Dipl.-Chem.

80538 MÜNCHEN
Prinzregentenstraße 16
Telefon (089) 21 23 99 0
Telefax (089) 21 23 99 22
E-Mail info@lederer-keller.de

09.12.2003
T/en

Helm AG
Nordkanalstraße 28
20097 Hamburg

Pharmaceutical formulation of valaciclovir

This invention relates to a pharmaceutical formulation of valaciclovir.

The compound 9-[(2-hydroxyethoxy)methyl]guanine, otherwise known as acyclovir possesses potent antiviral activity and is widely used in the treatment and prophylaxis of viral infections in humans, particularly infections caused by the herpes group of viruses (see, for example, Schaeffer et al, Nature, 272, 583 – 585 (1978), UK Patent No. 1523865, US Patent No. 4,199,574). However, acyclovir is poorly absorbed from the gastrointestinal tract upon oral administration and this low bioavailability means that multiple high doses of oral drug may need to be administered, especially for the treatment of less sensitive viruses or infections in order to achieve and maintain effective anti-viral levels in the plasma.

The L-valine ester of acyclovir (2-[2-amino-1,6-dihydro-6-oxopurin-9-yl)methoxy]ethyl L-valinate (herein referred to as valaviclovir) has been shown to possess much improved bioavailability whilst retaining the anti-viral properties of acyclovir. A preferred form of this compound is its hydrochloride salt which is herein referred to as valaciclovir hydrochloride. Valaciclovir and its salts including the hydrochloride salt are disclosed in US Patent No. 4,957,924, European Patent No. 0308065 and Beauchamp et al, Antiviral Chemistry and Chemotherapy, 3(3), 157 – 164 (1992). Tablets of valaciclovir are also generally disclosed in the US Patent No. 4, 957, 924 and European Patent No. 0308065.

WO 96/22082 discloses valaciclovir tablets containing colloidal silicon dioxide. The colloidal silicon dioxide is added to provide a robust tablet formulation being capable of consistently providing tablets substantially free of cracks and having a hardness such that the tablet not only has an acceptable crushing force but also does not break during tumbling.

Colloidal silicon dioxide is also known as flow regulating agent (Fiedler, Lexikon der Hilfsstoffe, Editio Cantor Verlag, 5. Aufl., 2002; Schmidt, Christin, Wirk- und Hilfsstoffe für Rezeptur, Defektur und Großherstellung, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1999).

Good flow is a prerequisite for a successful manufacture of for example tablets and powder-filled capsules on a production scale. The physical flow properties and densities in particular of tabletting powders are of great technical importance as tabletting machines usually are filled in volumetrically. The weight of the resulting tablet is thus depending on the dies of the tabletting machine and the densities of the related powders. If the powder is showing great differences in bulk and tapped densities great variations in the filling/dosing of the tabletting machines will occur (Bauer, Frömming, Führer: Pharmazeutische Technologie, 1993, Georg Thieme Verlag, Stuttgart). Thus, in the preparation of pharmaceutical formulations good physical flow properties and low differences in bulk and tapped densities of the compositions used for the preparation of the pharmaceutical formulations are desirable.

During development of pharmaceutical formulations containing valaciclovir, often difficulties in the physical flow properties of the composition are encountered.

It is therefore an object of the invention to provide a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof which does not encounter the above problems. In particular the formulation should be preparable from a composition having good physical flow properties and low differences in bulk and tapped densities.

It has now been found that the above problems can be overcome by adding titanium dioxide to the composition in the preparation of the pharmaceutical formulation.

Thus, the present invention relates to a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof, characterized in that the formulation comprises titanium dioxide.

The pharmaceutical formulation of the present invention is a solid, preferably oral composition, such as tablets, capsules, granules, pellets or sachets. Particularly preferred the pharmaceutical formulation is in the form of tablets.

The titanium dioxide is preferably present in the pharmaceutical formulation in an amount of 0.05 to 3 wt.%, more preferably in an amount of 0.5 to 1.5 wt.% of the total weight of the formulation.

It has been found that advantageous properties regarding density, compressibility and flowability of the ingredient mixture before tabletting and regarding hardness and disintegration of the resulting tablets can be obtained if a highly dispersed titanium dioxide is employed. Such highly dispersed titanium dioxide has for example an average primary particle size in the range of 16 to 26 nm, preferably of about 21 nm. The specific surface area (BET) of the titanium dioxide can typically be in the range of 30 to 70 m^2/g, preferably 50 ± 15 m^2/g. The tapped density of the titanium dioxide according to DIN ISO 787/XI, Aug. 1983, can be in the range of 120 to 140 g/l, preferably about 130 g/l. The titanium dioxide can be a hydrophilic fumed titanium dioxide.

A preferred titanium dioxide with the above physical properties is a hydrophilic fumed titanium dioxide sold by Degussa under the trademark AEROXIDE® TiO_2 P 25. A further titanium dioxide grade which may be used in the pharmaceutical formulation of the present invention is TiO_2 P 25 S. Two or more different grades of titanium dioxide may be used within one formulation.

The pharmaceutical formulation of the present invention may comprise any suitable amount of the active ingredient, valaciclovir or a pharmaceutically acceptable salt thereof. Advantageously the formulation contains a high proportion of valaciclovir, such as at least 50 wt.%, more preferably at least 75% wt.% of the total weight of the formulation.

Preferably the pharmaceutical formulation comprises a pharmaceutically acceptable salt of valaciclovir, in particular valaciclovir hydrochloride.

The pharmaceutical formulation of the present invention may further comprise one or more pharmaceutically acceptable excipients, such as fillers, binding agents, lubricants and disintegrating agents.

As fillers conventional fillers known to the person skilled in the art may be used. Suitable fillers are for example lactose, starch and various celluloses. The amount of the fillers present in the pharmaceutical formulation is not particularly limited and can be, for example, in the range of 0 to 30 wt.%, preferably 10 to 20 wt.% of the total weight of the formulation.

The binding agent serves, for example to bind the particles together and improve tablet hardness. Preferably the binding agent is present in an amount of 1 to 5 wt.%, more preferably at 2 to 4 wt.% of the total weight of the formulation. The binding agent can for example be methylcellulose or more preferably povidone. The grade of povidone is advantageously K30.

The binding agent such as povidone can be added dry to the drug and other pharmaceutically acceptable excipients and then a granulating solvent (such as water or an alcohol, in particular ethanol) can be added, but preferably it is dissolved in the granulating solvent before adding to the drug.

The lubricant is suitably present in an amount of 0.1 to 2 wt.%, preferably about 1 wt.% of the total weight of the formulation. Although lubricants such as talc or sodium lauryl sulfate are suitable, preferably the lubricant is a stearate, more preferably an alkali metal stearate, such as magnesium stearate.

Although valaciclovir is very soluble, especially in its salt form, it is preferable if a disintegrating agent is present in the pharmaceutical formulation, suitably in an amount of 0.1 to 20 wt.%, more preferably at about 0.5 to 7 wt.% of the total weight of the formulation. For example, crosscarmellose sodium may be used as disintegrating agent or any other suitable disintegrating agent known to the person skilled in the art.

The present invention also provides the use of titanium dioxide for the manufacture of a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof.

A further aspect of the present invention provides a process of preparing a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof, comprising admixing valaciclovir or a pharmaceutically acceptable salt thereof with titanium dioxide and optionally with further pharmaceutically acceptable excipients. Advantageously the valaciclovir or a pharmaceutically acceptable salt thereof is admixed with at least part of the pharmaceutically acceptable excipients, the mixture is granulated and the granulates are mixed with the titanium dioxide and, if applicable, the remainder of the pharmaceutically acceptable excipients. The obtained mixture can then be tabletted.

In a preferred embodiment of the process of the present invention granules are formed by mixing valaciclovir or a pharmaceutically acceptable salt thereof with the filler and a solution of the binding agent in a granulating solvent such as water or an alcohol (preferably ethanol) and granulating the obtained mixture to form granules; drying the granules; blending the dried granules with the lubricant, the disintegration enhancer and the titanium dioxide; and then compressing the blended mixture to form a tablet.

The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

The invention is now illustrated in the following examples which are not to be construed as being limiting.

Examples

Tablets of the following formulations 1 – 3 were prepared by granulating 1, 2 and 3 with a solution of 4 in 5. After drying 6, 7 and, where applicable, 8 were added. The final mixture was further processed to tablets with a final weight of 700,0 mg.

Formulation 1:

1) Valaciclovir HCl	556,24 mg
2) Pregelatinized Starch	70,0 mg
3) Lactose monohydrate	34,26 mg
4) Povidone K30	21,00 mg
5) Alcohol	378,0 mg
6) Crosscarmellose Sodium	4.50 mg

7) Magnesium Stearate	7.00 mg
8) TiO_2 P 25 / TiO_2 P 25 S	7.00 mg

Formulation 2:

1) Valaciclovir HCl	556,24 mg
2) Pregelatinized Starch	70,0 mg
3) Lactose monohydrate	41,26 mg
4) Povidone K30	21,00 mg
5) Alcohol	378,0 mg
6) Crosscarmellose Sodium	4.50 mg
7) Magnesium Stearate	7.00 mg

Formulation 3:

1) Valaciclovir HCl	556,24 mg
2) Pregelatinized Starch	70,0 mg
3) Lactose monohydrate	34,26 mg
4) Povidone K30	21,00 mg
5) Alcohol	378,0 mg
6) Crosscarmellose Sodium	4.50 mg
7) Magnesium Stearate	7.00 mg
8) SiO_2	7.00 mg

The following physical parameters of the final mixtures and the obtained tablets were measured:

Hausner Factor

The Hausner Factor is calculated by the following formula:

$$\frac{\text{bulk density}}{\text{tapped density}}$$

The bulk density is measured according to Ph Eur 2.9.15 (European Pharmacopoeia, 4. Ed., published by the Directorate for the Quality of Medicines of the Council of Europe) as poured density. The tapped density is measured according to Ph Eur 2.9.15.

The Hausner Factor is a measure for the flowability/compressibility of powders and should be around 1. Preferably mixtures for preparing tablets should have a Hausner Factor of <1.16.

Compressibility Index

The compressibility index is calculated by the formula:

$$\frac{100\ (V_0-V_{300})}{V_0}$$

wherein V_0 is the bulk volume and V_{300} is the tapped volume of the mixture, both measured as described in W. A. Ritschel and A. Bauer-Brandl, Die Tablette, p. 355f, 2. Ed., Editio Cantor Verlag, Aulendorf, 2002.

A compressibility below 15% indicates a good flow, above 25% a difficult flow.

Flowability

The flowability is measured according to Ph Eur 2.9.16.

Pile angle

Approximately 50 g sample is taken and the flowability test is applied as described above. The sample that comes out from the funnel is collected over a clean paper without changing the conical shape of the collected sample. Firstly the surroundings of this cone is drawn on the paper to determine the diameter. Secondly the height (=h) of this cone is measured by means of a thin pipe. The diameter of the circle on the paper is measured and recorded (=D). To obtain the radius of the circle the diameter is divided by two (D/2=r).

After obtaining the r and h values the following equation is used to calculate the pile angle:

$$\text{pile angle (Tan } \alpha) = \frac{\text{Height (h)}}{\text{Radius (r)}}$$

A pile angle $\alpha \leq 30°$ indicates good flow, a pile angle of $30° < \alpha \leq 40°$ indicates a difficult flow and a pile angle of $\alpha > 40°$ indicates a very bad flow.

Hardness

Tablets should have a high hardness to avoid break during tumbling. The hardness is measured according to Ph Eur 2.9.8.

Disintegration

The time required for disintegration of the tablets is measured according to Ph Eur 2.9.1. For immediate release tablets the time should be <15 min.

The results of the measurements are summarized in the following table:

	Formulation 1	**Formulation 2**	**Formulation 3**
Hausner Factor	1.14	1.41	1.31
Compressibility Index	12,61%	25,61%	23,8%
Flowability	4 sec.	19 sec.	15 sec.
Pile angle (α)	30.1°	40,5°	34,2°
Hardness	180 N	90 N	130 N
Disintegration	12'15" – 14'10"	17'15" – 22'10"	16'20" – 18'20"

The above results show that by adding titanium dioxide a tablet mass (formulation 1) with very good flow properties and thus very good tabletting behaviour is obtained. The tablets prepared from this mass have a high hardness and at the same time a short disintegration time. On contrary, as shown with formulations 2 and 3, the "classic" flow regulating agent SiO_2 (formulation 3) does not give comparably good results, although they are still better than without adding any flow regulating agent (formulation 2).

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Claims

1. Pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof, characterized in that the formulation comprises titanium dioxide.

2. Pharmaceutical formulation according to claim 1, said formulation being in the form of tablets, capsules, granules, pellets or sachets.

3. Pharmaceutical formulation according to any of the proceeding claims, wherein the titanium dioxide is present in an amount of 0.05 to 3 wt.% of the total weight of the formulation.

4. Pharmaceutical formulation according to claim 3, wherein the titanium dioxide is present in an amount of 0.5 to 1.5 wt.% of the total weight of the formulation.

5. Pharmaceutical formulation according to any of the proceeding claims, wherein the titanium dioxide is a highly dispersed titanium dioxide.

6. Pharmaceutical formulation according to claim 5, wherein the titanium dioxide has an average primary particle size in the range of 16 to 26 nm, preferably of about 21 nm.

7. Pharmaceutical formulation according to any of the proceeding claims, wherein the valaciclovir or a pharmaceutically acceptable salt thereof is present in an amount of at least 50 wt.% of the total weight of the formulation.

8. Pharmaceutical formulation according to any of the proceeding claims, further comprising one or more pharmaceutically acceptable excipients, such as fillers, binding agents, lubricants and disintegrating agents.

9. Use of titanium dioxide for the manufacture of a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof.

10. Process of preparing a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof, comprising admixing valaciclovir or a pharmaceutically acceptable salt thereof with titanium dioxide and optionally with further pharmaceutically acceptable excipients.

11. Process according to claim 10 wherein the valaciclovir or a pharmaceutically acceptable salt thereof is admixed with at least part of the pharmaceutically acceptable excipients, the mixture is granulated and the granulates are mixed with the titanium dioxide and, if applicable, the remainder of the pharmaceutically acceptable excipients.

12. Process according to claim 11, further comprising the step of tabletting the obtained mixture.

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Abstract

The invention relates to a pharmaceutical formulation of valaciclovir or a pharmaceutically acceptable salt thereof and a process of preparing such formulation.